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| EXAMINER | |
|---|---|
| SZNAIDMAN, MARCOS L | |
| **ART UNIT** | **PAPER NUMBER** |
| 1611 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/522,258 | LICHTENBERG ET AL. | |
| | Examiner | Art Unit | |
| | MARCOS SZNAIDMAN | 4173 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *12-32* is/are pending in the application.

4a) Of the above claim(s) *14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-27,31 and 32* is/are rejected.

7)☐ Claim(s) *28-30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of claims*

Addition of claims 23-32, in the reply filed on January 3, 2008, is acknowledged.

Claims 12-32 are currently pending and are the subject of this office action.

Claim 14 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on August 24, 2007.

Claims 12-13, and 15-32 are presently under examination.

Applicant's amendment of claims 12, 16 and 18, in the reply filed on January 3, 2008, is acknowledged.

### *Priority*

The present application claims priority to international application No. PCT/DK03/00518 filed 07/31/2003, and to foreign applications DENMARK PA 2003 00371 filed 03/11/2003, DENMARK PA 2002 01839 filed 11/28/2002 and DENMARK PA 2002 01165 filed 08/01/2002. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

### *Response to Arguments*

This is in response to applicant's arguments, filed on January 3, 2008.

***Claims rejected under 35 USC 112, first paragraph (enablement).***

Applicant's arguments have been fully considered and they are persuasive.

Rejection under 35 USC 112, first paragraph (enablement) is withdrawn.

***Claims rejected under 35 USC 103***

Applicant's arguments have been fully considered but they are not persuasive.

Applicant argues that: even though Dahl et al. (hereinafter "Dahl") describes a number of compounds active as chloride channel blockers, among them some of the compounds claimed in the present invention (including the elected species); they are silent about any use of the compounds for inhibition of angiogenesis and furthermore, are silent about any VRAC (Volume Regulated Anion Chanel) blocker activity of the compounds.

First, ion channels and in particular chloride ion channels are subdivided in several subtypes according to their gating mechanism: a- Voltage, b- Volume (VRAC), c- Ligand binding, etc. So, the general term: chloride channel, used by Dahl, is interpreted to be meant any of those groups, including VRACs. Even if Dahl would have specified that the compounds are Voltage Chloride channel blockers or any other subtype, since all these ion channels (Voltage, VRAC, ligand binding, etc) belong to the same family of chloride channels with similar structures, it would have been obvious to try any of the of the Voltage Chloride channel blockers or any other subtype blockers, as inhibitors of VRAC. In fact, Dahl teaches a potent inhibitor of chloride channel: 5-

nitro-2-(3-phenylpropylamino)benzoic acid (see page 5, under prior art), which is exactly the same compound that Manolopoulos describes as a chloride VRAC blocker (see abstract, line 4), which is consistent with the argument just presented: that any ion channel blocker of any of the subtypes, will be likely a blocker of any of the other subtypes. Although this is not always true, because some compounds are very selective, the point is, that it will be obvious for a person of ordinary skill in the art to try any blocker of any subtype of ion channel (Voltage, VRAC, ligand binding, etc) as a VRAC blocker or any other subtype of chloride channel blocker.

Second, it is true that Dahl is silent regarding angiogenesis, if that were not the case, this rejection would have been a 102 and not a 103. The association of these compounds (chloride VRAC or chloride channel blockers) with angiogenesis is made through Manolopoulos et. al. (hereinafter "Manolopoulos) that states that VRAC blockers are potent inhibitors of angiogenesis (see abstract).

Applicant further argues that Manolopoulos describes four VRAC blockers (chloride channel blockers) having a chemical structure very different from the Chloride channel blockers described by Dahl. This argument is not valid because, more than chemical similarity between compounds, what it is important is biological similarity. In other words, all these chemically diverse compounds bind to the same region, or to similar regions of the protein (chloride ion channel) causing the same effect (blocking a chloride ion channel), despite their structural diversity. The literature is full of examples, and is common knowledge, of enzymes and other proteins being blocked by structurally diverse compounds. Even though these compounds might be chemically different, the

enzyme or protein "sees" these compounds in a similar way, because in the three dimensional world of proteins, these structurally diverse compounds can have very similar three dimensional properties that are not obvious just by looking at their two dimensional structures on a piece of paper. A proof of the above statement is that the four structures mentioned by Manolopoulos (5-nitro-2-(3-phenylpropylamino)benzoic acid, mibrefadil, tamoxifen, and clomiphene are structurally very diverse, and despite that, they are all VRAC blockers.

Rejection under 35 USC 103 is maintained.

***Claims rejected under Double Patenting***

Since the 'provisional" nonstatutory obvious double patenting (ODP) rejection is not the only rejection remaining, the rejection is maintained. Applicant also is informed that the US filing date on record for the present application is: October 20, 2005, not January 25, 2005, as stated in the January 3, 2008 reply.

Rejections and/or objections not reiterated from previous office action are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

### *Claim Objections*

Claims 28-30 are objected to because of the following informalities: claim 28 depends on claim 29, claim 29 depends on claim 29 and claim 30 depends on claim 29. Appropriate correction is required.

Accordingly, these claims have not been further treated on the merits

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12-13, 15-27 and 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Manolopoulos (General Pharmacology 34 (2000) 107-116, cited by the applicant) in view of Dahl et. al. (WO 00/24707, cited by the applicant).

Claims 12-13,15-17 and 21, 23, 25-27, and 31-32 recite "a method of treatment, of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to inhibition of angiogenesis, comprising the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a compound of general formula I (specifically: N-3,5-di(trifluoromethyl)phenyl-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl]urea)."

Claims 18-20 and 22, 24 recite "a method of treatment of age-related macular degeneration of a living animal body, including a human, comprising the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a VRAC blocker or a pharmaceutically acceptable salt thereof (specifically: N-3,5-di(trifluoromethyl)phenyl-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl]urea)."

Manolopoulos teaches that "VRAC (a subclass of chloride channels) blockers are potent inhibitors of angiogenesis and thus might serve as therapeutic tools in tumor growth and other angiogenesis dependent diseases (see abstract). Manolopoulos does not teach the specific use of N-3,5-di(trifluoromethyl)phenyl-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl]urea for the treatment of angiogenesis dependent diseases. However, Dahl et. al. teach that compounds of general structure I (see abstract) and in particular of N-3,5-di(trifluoromethyl)phenyl-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl]urea (see page 36, 4$^{th}$ compound from the top) are useful as chloride channel blockers (Volume-Regulated Anion Channels (VRAC) are a subclass of chloride channels).

Since Manolopoulos teaches that VRAC (a subclass of chloride channels) blockers are useful for treating angiogenesis dependent diseases, and since Dahl et. al. teach that N-3,5-di(trifluoromethyl)phenyl-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl]urea is a chloride channel blocker (e.g. VRAC blocker) ; at the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to select any chloride channel inhibitor (in this case N-3,5-di(trifluoromethyl)phenyl-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl]urea) for treating any angiogenesis dependent disease (including those recited in claim 16 or age-related macular degeneration recited in claim 18 (see Manolopoulos, first paragraph of the introduction where he recites many pathological processes associated with angiogenesis: diabetic retinopathy, arthritis, inflammation and the growth of several types of solid tumors), thus resulting in the practice of claims 12-13, 15-27 and 31-32 with a reasonable expectation of success.

## *Double Patenting*

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 12-13, 15-27 and 31-32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 21-22, 35, and 38-39 of copending Application No. 10/526,208. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications claim identical set of compounds (elected species N-3,5-di(trifluoromethyl)phenyl-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl]urea is a species of the Markush formulas I of claim 21 and of formula II of claim 22 of application No. 10/526,208), for identical methods of use: for example: disease or condition is responsive to the blockade of chloride ion channels (in claim 35 of application No. 10/526,208), and disorder or condition responsive to inhibition of angiogenesis (in claim 38 of application No. 10/526,208) or the method wherein the disease, disorder or condition responsive to the blockade of chloride channels is.... (see list of diseases in claim 39 of application No. 10/526,208).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

### *Conclusion*

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

### *Correspondence*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is

(571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward can be reached on 571 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MLS
January 31, 2008

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